PATENT SPECIFICATION (11) 1 512 194

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(21) Application No. 6215/77 (22) Filed 15 Feb. 1977
(31) Convention Application No. 1070/76
(32) Filed 16 Feb. 1976 in
(33) Austria (AT)
(44) Complete Specification published 24 May 1978
(51) INT CL² C07D 295/12; A61K 31/535
(52) Index at acceptance
C2C 1562 215 220 22Y 246 255 25Y 270 271 27X 280 282 29X 29Y 30Y 311 313 314 315 31Y 328 332 334 338 342 34Y 579 603 621 62X 661 669 694 697 700 790 79Y KF KT KV NV

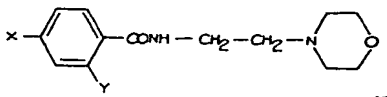
(19)

(54) BENZAMIDES

(71) We, F. HOFFMANN-LA ROCHE & CO., AKTIENGESELLSCHAFT, a Swiss Company of 124—184 Grenzacherstrasse, Basle, Switzerland, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention relates to benzamides. More particularly, the invention is concerned with benzamide derivatives, a process for the manufacture thereof and pharmaceutical preparations containing same.

The benzamide derivatives provided by the present invention are compounds of the general formula



(I)

wherein X represents a halogen atom or a trifluoromethyl or C_{3-4}-alkyl group and Y represents a hydrogen or halogen atom or a nitro group,

and N-oxides and acid addition salts thereof.

A halogen atom denoted by X or Y is a chlorine, fluorine, bromine or iodine atom. A C_{3-4}-alkyl group is a straight-chain or branched-chain alkyl group containing 3 or 4 carbon atoms, namely n-propyl, isopropyl, n-butyl, isobutyl, 1-methylpropyl or t-butyl.

The compounds of formula I form addition salts with organic or inorganic acids at the nitrogen atom of the morpholino radical. Examples of such salts are hydrohalides (e.g. hydrochlorides), phosphates, alkylsulphonates (e.g. ethanesulphonates), monoarylsulphonates (e.g. toluenesulphonates), acetates, citrates, benzoates and the like.

Preferred benzamide derivatives provided by this invention are those in which X represents a halogen atom. Also preferred are those benzamide derivatives in which Y represents a hydrogen atom or a nitro group.

The following are particularly preferred benzamide derivatives of this invention:

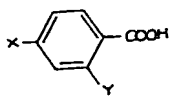
p - Chloro - N - (2 - morpholinoethyl)-benzamide,
p - fluoro - N - (2 - morpholinoethyl)-benzamide,
p - bromo - N - (2 - morpholinoethyl)-benzamide,
p - iodo - N - (2 - morpholinoethyl)-benzamide,
4 - chloro - N - (2 - morpholinoethyl) - 2-nitrobenzamide.

Other preferred benzamide derivatives of this invention are:

α,α,α - Trifluoro - N - (2 - morpholinoethyl)-p-toluamide,
p - t - butyl - N - (2 - morpholinoethyl)-benzamide,
2,4 - dichloro - N - (2 - morpholinoethyl)-benzamide,
p - chloro - N - (2 - morpholinoethyl)-benzamide N'-oxide.

According to the process provided by the present invention, the aforementioned benzamide derivatives (i.e. the compounds of formula I and N-oxides and acid addition salts thereof) are manufactured by

(a) reacting N - (2 - aminoethyl) - morpholine with an acid of the general formula

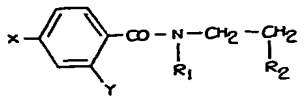


(II)

wherein X and Y have the significance given earlier,

or with a reactive functional derivative thereof, or

(b) reacting morpholine with a compound of the general formula

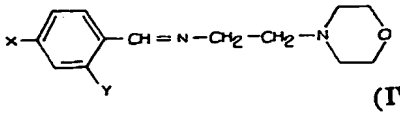


(III)

wherein X and Y have the significance given earlier, R_1 represents a hydrogen atom and R_2 represents a halogen atom, or R_1 and R_2 together represent an additional bond,

or

(c) oxidising a compound of the general formula

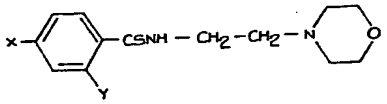


(IV)

wherein X and Y have the significance given earlier,

or

(d) converting a thioamide of the general formula



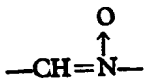
(V)

wherein X and Y have the significance given earlier,

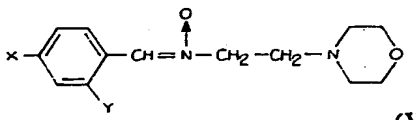
into the corresponding amide,

or

(e) converting the grouping



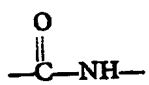
in a nitrone of the general formula



(VI)

wherein X and Y have the significance given earlier,

into the grouping



and, if desired, oxidising a resulting compound of formula I to the corresponding N-oxide or converting a resulting compound of formula I into an acid addition salt.

Examples of reactive functional derivatives of the acids of formula II are halides (e.g. chlorides), symmetric or mixed anhydrides, esters (e.g. methyl esters, p-nitrophenyl esters or N-hydroxysuccinimide esters), azides and amides (e.g. imidazolides or succinimides).

The reaction of N - (2 - aminoethyl)-morpholine with an acid of formula II or a reactive functional derivative thereof according to embodiment (a) of the present process can be carried out according to methods which are customary in peptide chemistry. Thus, for example, a free acid of formula II can be reacted with N - (2 - aminoethyl) - morpholine in the presence of a condensation agent in an inert solvent. If a carbodiimide (e.g. dicyclohexylcarbodiimide) is used as the condensation agent, the reaction is appropriately carried out in ethyl acetate, dioxan, methylene chloride, chloroform, benzene, acetonitrile or dimethylformamide at a temperature between about −20°C and room temperature, preferably at about 0°C. If phosphorus trichloride is used as the condensation agent, the reaction is appropriately carried out in a solvent such as pyridine at a temperature between about 0°C and the reflux temperature of the reaction mixture, preferably at about 90°C. In another aspect of embodiment (a), N - (2 - aminoethyl) - morpholine is reacted with one of the above-mentioned reactive functional derivatives of an acid of formula II. Thus, for example, a halide (e.g. the chloride) of an acid of formula II can be reacted with N - (2-aminoethyl) - morpholine in the presence of a solvent (e.g. diethyl ether, pyridine or water) at about 0°C.

The compounds of formula III in which R_1 represents a hydrogen atom and R_2 represents a halogen atom are N - (2 - haloethyl)-benzamides such as p - chloro - N - (2-chloroethyl) - benzamide and the like. The compounds of formula III in which R_1 and R_2 together represent an additional bond are benzoylaziridines (e.g. p - chloro - benzoylaziridine and the like).

According to embodiment (b) of the present process morpholine can be reacted in a manner known per se with a compound of formula III at a temperature up to the reflux temperature of the reaction mixture, if desired in the presence of a solvent. If a benzoylaziridine of formula III is used, the reaction is preferably carried out at the reflux temperature of the reaction mixture in the presence of an inert solvent (e.g. toluene, acetone or benzene). If a N - (2 - haloethyl) - benzamide of formula III is used, the reaction is preferably carried out at a temperature of about 100°C.

The oxidation of a compound of formula IV according to embodiment (c) of the present process can be carried out in a manner known per se using an oxidising agent such as hydrogen peroxide, potassium permanganate, an

organic peracid (e.g. peracetic acid) or a compound which releases hydrogen peroxide on solution in water (e.g. an alkali metal peroxide or persulphuric acid). The oxidation is appropriately carried out in an inert solvent, (e.g. methanol, ethanol or acetone).

The conversion of a thioamide of formula V into the corresponding amide of formula I according to embodiment (d) of the present process can be carried out in a manner known per se, for example using lead tetraacetate in an inert solvent (e.g. water) at a temperature up to the reflux temperature of the reaction mixture, or also using 1,2-butylene oxide, if appropriate in an inert solvent such as a lower alkanol (e.g. methanol) at a temperature up to the reflux temperature of the reaction mixture.

The conversion of a nitrone of formula VI into a compound of formula I according to embodiment (e) of the present process can be carried out in a manner known per se, for example in the presence of acetic anhydride or acetyl chloride, if appropriate in a solvent such as glacial acetic acid at a temperature up to the reflux temperature of the reaction mixture, preferably at about 90°C.

A compound of formula I can be converted in a manner known per se into the corresponding N-oxide using an oxidising agent such as hydrogen peroxide or a peracid (e.g. peracetic acid) in a solvent such as glacial acetic acid at a temperature between about 0°C and 50°C, preferably at room temperature.

The starting materials of formulae II, III, IV, V and VI are known or analogues of known compounds and can be prepared by methods known per se.

The compounds of formula I, their N-oxides and acid addition salts have monoaminooxidase (MAO) inhibiting activity. Because of this activity, the compounds of formula I, their N-oxides and pharmaceutically acceptable acid addition salts can be used for the treatment of depressive conditions.

The MAO inhibiting activity of the compounds of the present invention can be determined using standard methods. Thus the compounds to be tested were administered p.o. to rats. One hour thereafter the animals were killed and the MAO inhibiting activity in the liver homogenates was measured according to the method described in Biochem. Pharmacol. 12 (1963) 1439—1441. The activity thus determined of representative compounds of the present invention and their toxicity can be seen from the ED_{50} values (μmol/kg, p.o. in rats) and LD_{50} values (mg/kg, p.o. in mice) listed in the following Table:

TABLE

Compound	ED_{50}	LD_{50}
p-Chloro-N-(2-morpholinoethyl)-benzamide	5	
α,α,α-Trifluoro-N-(2-morpholinoethyl)-p-toluamide	16	1000 – 2000
p-t-Butyl-N-(2-morpholinoethyl)-benzamide	16	1250 – 2500
p-Fluoro-N-(2-morpholinoethyl)-benzamide	14	1250 – 2500
p-Bromo-N-(2-morpholinoethyl)-benzamide	6	1250 – 2500
p-Iodo-N-(2-morpholinoethyl)-benzamide	4	1250 – 2500
2,4-Dichloro-N-(2-morpholinoethyl)-benzamide	13	1250 – 2500
4-Chloro-N-(2-morpholinoethyl)-2-nitrobenzamide	2	

The toxicity of p - chloro - N - (2 - morpholinoethyl) - benzamide expressed in LD_{50} (mg/kg, p.o. in rats) is 707±55 after 10 days.

The compounds of formula I, their N-oxides and their pharmaceutically acceptable acid addition salts can be used as medicaments in the form of pharmaceutical preparations which contain them in association with a compatible pharmaceutical carrier material. This carrier material can be an organic or inorganic inert carrier material which is suitable for enteral (e.g. oral) or parenteral administration (e.g. water, gelatine, gum arabic, lactose, starch, magnesium stearate, talc, vegetable oils, polyalkylene glycols etc). The pharmaceutical preparations can be made up in a solid form (e.g. as tablets, dragées, suppositories or capsules) or in a liquid form (e.g. as solutions, suspensions or emulsions). They may be sterilised and/or may contain compatible adjuvants such as preservatives, stabilising

agents, wetting agents, emulsifying agents, salts for modifying the osmotic pressure or buffering agents. They can also contain other therapeutic substances.

Appropriate pharmaceutical dosage forms contain ca 1 to 100 mg of a compound of formula I, a N-oxide thereof or a pharmaceutically acceptable acid addition salt thereof. Appropriate oral dosage ranges are from about 0.1 mg/kg per day to about 5 mg/kg per day. Appropriate parenteral dosage ranges are from about 0.01 mg/kg per day to about 0.5 mg/kg per day. These ranges can be extended upwards or downwards, depending on the individual requirement and the directions of the attending physician. Oral administration is preferred.

The following Examples illustrate the process provided by the present invention:

Example 1.

35 g of p-chlorobenzoyl chloride are added dropwise to a solution of 26 g of N-(2-aminoethyl)-morpholine in 200 ml of pyridine, whilst stirring and cooling with ice-water. Thereafter the mixture is stirred overnight at room temperature and subsequently evaporated to dryness. The residue is then evaporated twice more with 200 ml of toluene each time. The solid residue is taken up in 300 ml of ice-water and 300 ml of methylene chloride and rendered basic with 3—N sodium hydroxide solution. The phases are separated and the methylene chloride extract is washed with water, dried over sodium sulphate and evaporated to dryness. The residue is recrystallised from isopropanol. 41.5 g of p-chloro-N-(2-morpholinoethyl)-benzamide, melting point 137°C, are obtained.

The following compounds were manufactured in an analogous manner:

α,α,α - Trifluoro - N - (2 - morpholinoethyl) - p - toluamide, melting point 120°C to 121°C;

p - t - butyl - N - (2 - morpholinoethyl)-benzamide, melting point 94°C;

p - fluoro - N - (2 - morpholinoethyl)-benzamide, melting point 136°C to 137°C;

p - bromo - N - (2 - morpholinoethyl)-benzamide, melting point 140°C to 141°C;

p - iodo - N - (2 - morpholinoethyl)-benzamide, melting point 160°C;

2,4 - dichloro - N - (2 - morpholinoethyl)-benzamide, melting point 120°C.

Example 2.

13 g of N - (2 - aminoethyl) - morpholine are added dropwise to a solution of 17.5 g of p-chlorobenzoyl chloride in 100 ml of diethyl ether, whilst stirring and cooling with ice-water. After complete addition the mixture is stirred for 2 hours at room temperature. The crystalline product is filtered off and washed with diethyl ether. 9.1 g of p-chloro-N-(2-morpholinoethyl) - benzamide hydrochloride, melting point 207°C to 208°C, are obtained after recrystallisation from isopropanol.

4 - Chloro - N - (2 - morpholinoethyl)-2-nitrobenzamide hydrochloride, melting point 208°C was manufactured in an analogous manner.

Example 3.

10.5 g of p-chlorobenzoic acid anhydride are added portionwise to a solution of 4.55 g of N - (2 - aminoethyl) - morpholine in 100 ml of pyridine, whilst stirring and cooling with ice-water. After complete addition the mixture is stirred overnight at room temperature and subsequently evaporated to dryness. The residue is then evaporated twice more with 100 ml of toluene each time. The solid residue is taken up in 200 ml of methylene chloride and 200 ml of water and rendered basic with 3—N sodium hydroxide solution. The phases are separated and the methylene chloride extract is washed with water, dried over sodium sulphate and evaporated. The residue is recrystallised from isopropanol. 4.5 g of p-chloro - N - (2 - morpholinoethyl) - benzamide are obtained, which is identical to the product obtained in Example 1.

Example 4.

5.3 ml of chloroformic acid ethyl ester are added dropwise to a solution of 8.6 g of p-chlorobenzoic acid and 7.6 ml of triethylamine in 150 ml of acetone, whilst stirring and cooling with ice-water. After one hour at 0°C, a solution of 6.5 g of N - (2 - aminoethyl)-morpholine in 50 ml of acetone is added dropwise to the mixture and the mixture is then stirred overnight at room temperature. Thereafter it is concentrated, allowed to stand for 2 hours in the refrigerator and then filtered. The filtrate is evaporated to dryness and the residue is taken up in 250 ml of water and 250 ml of methylene chloride. The phases are separated and the methylene chloride extract is dried over sodium sulphate and evaporated. The residue is recrystallised from isopropanol. 7.8 g of p - chloro - N - (2-morpholinoethyl) - benzamide are obtained, which is identical to the product obtained in Example 1.

Example 5.

8.2 g of p - chlorobenzoic acid methyl ester and 6.25 g of N - (2 - aminoethyl) - morpholine are stirred together for 6 hours at 120°C. The mixture is then cooled to room temperature and 40 ml of diethyl ether are added. The mixture is then left to stand overnight in the refrigerator. The crystalline product is filtered off, washed with diethyl ether and recrystallised from isopropanol. 2.6 g of p - chloro - N - (2 - morpholinoethyl)-benzamide are obtained, which is identical to the product obtained in Example 1.

Example 6.

5.55 g of p-chlorobenzoic acid p-nitrophenyl ester are added to a solution of 2.6 g of N - (2 - aminoethyl) - morpholine in 100 ml of tetrahydrofuran and the mixture is allowed to stand overnight at room temperature. It is then evaporated to dryness and the residue is taken up in 200 ml of methylene chloride. The methylene chloride solution is washed three times with 50 ml of a 1% sodium hydroxide solution each time and twice with 50 ml of water each time until neutral, dried over sodium sulphate and evaporated to dryness. The residue is recrystallised from isopropanol. 3.1 g of p - chloro - N - (2-morpholinoethyl) - benzamide are obtained, which is identical to the product obtained in Example 1.

Example 7.

2.4 g of N - (p - chlorobenzoyl) - succinimide are added to a solution of 1.3 g of N - (2 - aminoethyl) - morpholine in 100 ml of dioxan and the mixture is stirred overnight at room temperature. It is then evaporated to dryness. 50 ml of ice-water are added to the oily residue and the crystallising mixture is allowed to stand overnight in the refrigerator. The product is filtered off, washed with cold water, dried and recrystallised from isopropanol. 0.65 g of p - chloro - N - (2 - morpholinoethyl) - benzamide is obtained, which is identical to the product obtained in Example 1.

Example 8.

7.8 g of p-chlorobenzoic acid and 6.5 g of N - (2 - aminoethyl) - morpholine are dissolved in 150 ml of pyridine. 10.5 g of dicyclohexylcarbodiimide are added at 4°C and the mixture is stirred for 4 hours at 4°C and overnight at room temperature. The mixture is then poured into 1 litre of water and the dicyclohexylurea formed is filtered off. The filtrate is extracted twice with 200 ml of methylene chloride each time. The methylene chloride extract is dried over sodium sulphate, evaporated to dryness and the residue recrystallised from isopropanol. 0.6 g of p-chloro - N - (2 - morpholinoethyl) - benzamide is obtained, which is identical to the product obtained in Example 1.

Example 9.

2.8 g of phosphorus trichloride in 20 ml of pyridine are added to 5.2 g of N-(2-aminoethyl)-morpholine in 80 ml of pyridine at −5°C over a period of 15 minutes, whilst stirring. The mixture is stirred for 30 minutes at −5°C and 90 minutes at room temperature. 3.1 g of p-chlorobenzoic acid are then added and the mixture is heated for 3 hours at 90°C. It is then evaporated to dryness and the residue is evaporated twice more with 100 ml of toluene each time. The solid residue is taken up in 100 ml of methylene chloride and 100 ml of ice-water and the mixture is rendered basic with 3—N sodium hydroxide solution. The phases are separated and the methylene chloride extract is washed with water, dried over sodium sulphate and evaporated. The residue is recrystallised from isopropanol. 1.3 g of p - chloro - N - (2-morpholinoethyl) - benzamide are obtained, which is identical to the product obtained in Example 1.

Example 10.

55.4 g of p-chlorobenzoylaziridine and 26.5 g of morpholine are boiled in 250 ml of toluene for 2 hours under reflux. The solution is then cooled to room temperature, whereupon crystals separate out. The crystallising solution is allowed to stand overnight in the refrigerator. Thereafter the product is filtered off, washed with toluene and recrystallised from isopropanol. 75.9 g of p - chloro - N - (2-morpholinoethyl) - benzamide are obtained, which is identical to the product obtained in Example 1.

Example 11.

5.45 g of p - chloro - N - (2 - chloroethyl) - benzamide and 8.7 g of morpholine are stirred together for 2 hours at 100°C. The mixture is then cooled to room temperature and 50 ml of water are added. The mixture is then rendered basic with 10% ammonia solution and extracted three times with 50 ml of methylene chloride each time. The methylene chloride extract is dried over sodium sulphate and evaporated. The residue is chromatographed over a silica gel column with a mixture of chloroform and ethanol. The product is recrystallised from isopropanol. 2.2 g of p - chloro - N - (2 - morpholinoethyl)-benzamide are obtained, which is identical to the product obtained in Example 1.

Example 12.

26 g of p - chlorobenzaldehyde and 24 g of N - (2 - aminoethyl) - morpholine are boiled in 150 ml of benzene for 3 hours under reflux with water being separated. The mixture is then evaporated to dryness and the residue is distilled at 165°C/0.01 mm Hg. 5 g of the resulting 4 - [2 -[(p - chlorobenzylidene)-amino] - ethyl] - morpholine, 2.3 g of sodium acetate and 3 ml of 30% hydrogen peroxide are stirred in 60 ml of methanol overnight at room temperature. Thereafter the mixture is evaporated to dryness and the residue is taken up in 50 ml of methylene chloride and 50 ml of water. The phases are separated and the aqueous phase extracted with 50 ml of methylene chloride. The methylene chloride extract is dried over sodium sulphate and evaporated. The residue is chromatographed over a silica gel column with a mixture of chloroform and ethanol. The pure fractions are

combined and evaporated, and the residue recrystallised from isopropanol. 0.7 g of p-chloro - N - (2 - morpholinoethyl) - benzamide is obtained, which is identical to the product obtained in Example 1.

Example 13.

900 mg of p - chloro - N - (2 - morpholinoethyl) - thiobenzamide hydrochloride are boiled in 100 ml of water with 2 g of lead tetraacetate for 10 hours under reflux. The mixture is then filtered and the filtrate is evaporated to dryness. The residue is chromatographed over a silica gel column with a mixture of chloroform and ethanol. The product is recrystallised from isopropanol. 0.3 g of p - chloro - N - (2 - morpholinoethyl)-benzamide is obtained, which is identical to the product obtained in Example 1.

Example 14.

1.0 g of p - chloro - N - (2 - morpholinoethyl) - thiobenzamide hydrochloride is boiled in 100 ml of methanol with 35 ml of 1,2-butylene oxide for 14 hours under reflux. The mixture is evaporated to dryness and the residue recrystallised from isopropanol. 0.6 g of p - chloro - N - (2 - morpholinoethyl)-benzamide is obtained, which is identical to the product obtained in Example 1.

Example 15.

4.0 g of α - (p - chlorophenyl) - N - (2-morpholinoethyl) - nitrone are heated to 90°C in 15 ml of glacial acetic acid and 15 ml of acetic anhydride for 24 hours. The mixture is then cooled to room temperature, poured into 200 ml of ice-water and rendered basic with 20% sodium hydroxide solution. Thereafter the mixture is extracted twice with 100 ml of methylene chloride each time. The methylene chloride extract is washed with water, dried over sodium sulphate and evaporated. The residue is chromatographed over a silica gel column with a mixture of chloroform and ethanol. The product is recrystallised from isopropanol. 0.13 g of p-chloro - N - (2 - morpholinoethyl) - benzamide is obtained, which is identical to the product obtained in Example 1.

Example 16.

25 ml of 30% hydrogen peroxide are added to a solution of 10 g of p - chloro - N - (2-morpholinoethyl) - benzamide in 50 ml of glacial acetic acid and the mixture is allowed to stand for 48 hours at room temperature. The mixture is then evaporated to dryness and the residue chromatographed over a silica gel column with a mixture of chloroform and ethanol. The pure fractions are evaporated and the residue recrystallised from an ethyl acetate/isopropyl ether mixture. 6.8 g of p-chloro - N - (2 - morpholinoethyl) - benzamide N'-oxide, melting point 201°C (decomposition), are obtained.

The following Example illustrates a typical pharmaceutical preparation provided by this invention:

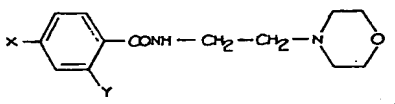
Example A.

Tablets of the following composition are manufactured in a manner known per se:

p-Chloro-N-(2-morpholino-ethyl)-benzamide	50	mg
Lactose	95	mg
Maize starch	100	mg
Talc	4.5	mg
Magnesium stearate	0.5	mg
Weight of one tablet	250.0	mg

WHAT WE CLAIM IS:—

1. Compounds of the general formula



(I)

wherein X represents a halogen atom or a trifluoromethyl or C_{3-4}-alkyl group and Y represents a hydrogen or halogen atom or a nitro group,

and N-oxides and acid addition salts thereof.

2. Benzamide derivatives according to claim 1, wherein X represents a halogen atom.

3. Benzamide derivatives according to claim 1 or claim 2, wherein Y represents a hydrogen atom or a nitro group.

4. p - Chloro - N - (2 - morpholinoethyl)-benzamide.

5. p - Iodo - N - (2 - morpholinoethyl)-benzamide.

6. p - Fluoro - N - (2 - morpholinoethyl)-benzamide.

7. p - Bromo - N - (2 - morpholinoethyl)-benzamide.

8. 4 - Chloro - N - (2 - morpholinoethyl)-2-nitrobenzamide.

9. 2,4 - Dichloro - N - (2 - morpholinoethyl)-benzamide.

10. α,α,α - Trifluoro - N - (2 - morpholinoethyl)-p-toluamide.

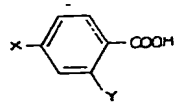
11. p - t - Butyl - N - (2 - morpholinoethyl)-benzamide.

12. p - Chloro - N - (2 - morpholinoethyl)-benzamide N'-oxide.

13. Acid addition salts of the compounds claimed in any one of claims 4 to 11 inclusive.

14. A process for the manufacture of the benzamide derivatives set forth in claim 1, which process comprises

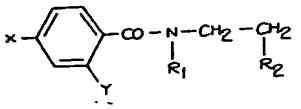
(a) reacting N - (2 - aminoethyl) - morpholine with an acid of the general formula



(II)

wherein X and Y have the significance given earlier,
or with a reactive functional derivative thereof,
or

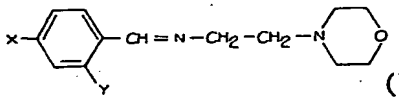
(b) reacting morpholine with a compound of the general formula



(III)

wherein X and Y have the significance given earlier, R_1 represents a hydrogen atom and R_2 represents a halogen atom, or R_1 and R_2 together represent an additional bond,
or

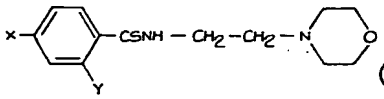
(c) oxidising a compound of the general formula



(IV)

wherein X and Y have the significance given earlier,
or

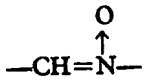
(d) converting a thioamide of the general formula



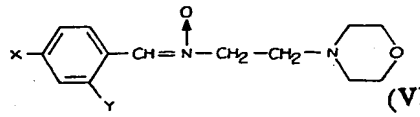
(V)

wherein X and Y have the significance given earlier,
into the corresponding amide,
or

(e) converting the grouping

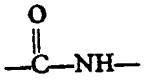


in a nitrone of the general formula



(VI)

wherein X and Y have the significance given earlier,
into the grouping



and, if desired, oxidising a resulting compound of formula I to the corresponding N-oxide or converting a resulting compound of formula I into an acid addition salt.

15. A process according to claim 14, wherein a starting material of formula II, III, IV, V or VI in which X represents a halogen atom is used.

16. A process according to claim 14 or claim 15, wherein a starting material of formula II, III, IV, V or VI in which Y represents a hydrogen atom or a nitro group is used.

17. A process according to any one of claims 14 to 16 inclusive, wherein a starting material of formula II, III, IV, V or VI in which X represents a chlorine atom and Y represents a hydrogen atom is used.

18. A process according to any one of claims 14 to 16 inclusive, wherein a starting material of formula II, III, IV, V or VI in which X represents an iodine atom and Y represents a hydrogen atom is used.

19. A process according to any one of claims 14 to 16 inclusive, wherein a starting material of formula II, III, IV, V or VI in which X represents a fluorine atom and Y represents a hydrogen atom is used.

20. A process according to any one of claims 14 to 16 inclusive, wherein a starting material of formula II, III, IV, V or VI in which X represents a bromine atom and Y represents a hydrogen atom is used.

21. A process according to any one of claims 14 to 16 inclusive, wherein a starting material of formula II, III, IV, V or VI in which X represents a chlorine atom and Y represents a nitro group is used.

22. A process according to claim 14 or claim 15, wherein a starting material of formula II, III, IV, V or VI in which X and Y each represent a chlorine atom is used.

23. A process according to claim 14 or claim 16, wherein a starting material of formula II, III, IV, V or VI in which X represents a trifluoromethyl group and Y represents a hydrogen atom is used.

24. A process according to claim 14 or claim 16, wherein a starting material of formula II, III, IV, V or VI in which X represents a t-butyl group and Y represents a hydrogen atom is used.

25. A process for the manufacture of the benzamide derivatives set forth in claim 1, substantially as hereinbefore described with reference to any one of Examples 1 to 16.

26. Benzamide derivatives as set forth in claim 1, when manufactured by the process claimed in any one of claims 14 to 25 inclusive or by an obvious chemical equivalent thereof.

27. A pharmaceutical preparation which contains a compound of formula I given in claim 1, or a N-oxide or pharmaceutically acceptable acid addition salt thereof in association with a compatible pharmaceutical carrier material.

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Printed for Her Majesty's Stationery Office by the Courier Press, Leamington Spa, 1978.
Published by the Patent Office, 25 Southampton Buildings, London, WC2A 1AY, from which copies may be obtained.